SUMMARIES OF REVIEW OF PESTICIDES CONSIDERED FOR USE IN THE GYPSY MOTH ERADICATION PROGRAM IN SANTA BARBARA COUNTY IN 1982

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* Additional detailed information is available for examination at the California Department of Food and Agriculture in Sacramento in the following reviews:

HS-725 Scientific Articles on Biological Effects of Carbaryl, (Rev. February 5, 1982 7 Volumes.

HS-975 Scientific Articles on Biologic Effects of Exposure to Diflubenzuron (Dimilin), (February 5, 1982), 3 Volumes.

HS-976 Scientific Articles on Biologic Effects of Exposure to Trichlorfon (Dylox), (February 5, 1982), 2 Volumes.

HS-977 Scientific Articles on Biologic Effects of Exposure to Acephate (Orthene), (February 5, 1982), 2 Volumes.

HS-978 Scientific Articles on Biologic Effects of Exposure to Methoxychlor, (February 5, 1982), 2 Volumes.

FIRST REVIEW - February 5, 1982

CHEMICAL PESTICIDES

Six chemical agents have been identified for potential use against gypsy moth infestations; a brief summary of the toxicity of these agents follows.

ACEPHATE
(ORTHENE)

Background

Orthene (acephate) is a broad spectrum organophosphate. It was introduced into the insecticide market by the Ortho Division of Chevron Chemical Company in the early 1970's. Since then, Acephate has been used several times to suppress outbreaks of spruce budworm in environmentally sensitive areas (Hydorn et al., 1979; Rabeni et al., 1979).

Toxic Potency

Oral LD_{50}'s for acephate are reported (Rojankovich et al., 1972; Zinkl et al., 1981) as follows:

male rats: 945 mg/kg
female rats: 866 mg/kg
dark-eyed juncos (a bird species): 106 mg/kg

The toxicity of acephate is not appreciably different via inhalation than the oral route (Berteau et al., 1978). Minimum lethal dose (MLD) in dogs was found to be 681 mg/kg. The minimum emetic dose (MED) in dogs is 215 mg/kg. Ninety-day feeding studies in rats and dogs showed no sign of abnormalities in physical or histopathological factors (CDFA). Rats dosed with low levels of acephate for 60 days at 5 mg/kg/day showed no alteration in the myogenic properties of smooth muscle (Whitcomb, 1979).

Biokinetics

Acephate is very water soluble, with a pK = 8.3. It is 97 percent ionized at pH = 6.5 (Duangsawsdi et al., 1979). The half-life ($t_{1/2}$) in plants and water was shown to be 5-10 days (Bart, 1979). Of the impurities isolated from acephate, O,O,S-trimethyl phosphorothioate showed slight potentiation of mouse toxicity when added to purified acephate (from 570 to 460 mg/kg). O,O-dimethyl N-acetylphosphoramidothioate caused a significant decrease in mouse toxicity (from 570 to 720 mg/kg), (Fukuto et al., 1977).

Specific Toxicity

Acephate was positive as a point mutagen in one test, being weakly mutagenic in Salmonella typhimurium. DNA damage in the form of enhanced mitotic recombination in S. cerevisiae and increased unscheduled DNA synthesis was also noted. In vivo mutagenesis testing (Drosophila sex-linked recessive lethal test) at 10 ppm acephate yielded negative results (Poole et al., 1977; Waters et al., 1981).

Acephate was nitrosated with sodium nitrite in vitro, and the nitrosated compound was tested for mutagenic activity in a bacterial spot test with S. typhimurium. Results were negative (Seiler, 1977).

Exposure Potential

Following aerial application at the rate of 0.57 kg acephate/ha for the control of spruce budworm, minor short-term perturbation to stream ecosystems occurred. Depression of brain cholinesterase activity occurred in birds (Zinkl et al., 1980).

The conversion of acephate to methamidophos was found to occur in fish, insects, and sediment, but not in flowing water (Geen et al., 1981). The degradation products in plants are 90-95% non-toxic salts and 5-10% O,S-dimethyl phosphoramindothioate. This latter compound is the primary active ingredient in another pesticide product marketed under the name "Monitor" (Bart, 1979).

The recommended aerial application rate for acephate is 2/3 to 1 lb. in 1/2 gallon water/acre. This is calculated to be 340.5 gm/acre, or 8.41 ug/cm^2.

CARBARYL (SEVIN)

Background

Carbaryl is the 1-naphthyl ester of N-methyl carbamic acid. It was introduced by Union Carbide Corporation in 1956 as an insecticide with a broad range of applications (Spencer, 1973). Carbaryl use represents approximately 10 percent of all agricultural insecticide use in the United States (USDA, 1974).

Toxic Potency

Carbaryl derives its efficacy from its ability to inhibit the enzyme cholinesterase, resulting in excess acetycholine at the endings of parasympathetic and motor nerves. The LD_{50} of carbaryl administered orally in various mammalian species has been reported as 250 to 850 mg/kg of body weight in the rat, 110 to 588 mg/kg in the mouse, 280 mg/kg in the guinea pig, 710 mg/kg in the rabbit, 250 to 795 mg/kg in the dog and 1,000 mg/kg in the monkey. A dermal LD_{50} of 4,000 mg/kg is reported for the rabbits (Mount and Oehme, 1981). In a 6-month oral study, monkeys showed little or no cholinesterase inhibition below 600 mg/kg (Serrone et al., 1966). Carbaryl is moderately toxic to fish and birds and is highly toxic to bees (Mount and Oehme, 1981).

Data from human exposure has shown that a single oral dose of 2.0 mg/kg carbaryl produced no objective signs of intoxication in human volunteers. One group of 5 men was given 0.13 mg/kg/day for 6 weeks with no evidence of deleterious action (Wills, 1968). A single oral dose of 250 mg(2.8 mg/kg)

caused a moderate degree of poisoning in one instance (Mount and Oehme, 1981). Literature suggests that low doses of carbaryl may have a detrimental effect on the kidney.

Biokinetics

The primary metabolism of carbaryl in man appears to involve hydrolysis (Knaak et al., 1965). In rats, 25 to 30 percent of a C^{14} labeled carbaryl dose was hydrolyzed, and 70 to 80 percent of the dose was excreted in urine within 24 hours (Mount and Oehme, 1981). When applied dermally, C^{14} labeled carbaryl applied to the forearm of human volunteers resulted in 73 percent absorption (Feldman and Mailbach, 1974). Carbaryl has shown a lack of persistence in body tissue.

Specific Toxicity

Teratogenic Effects: A 3 generation study of carbaryl added to the diet of rats showed that 10 mg/kg/day did not produce an effect on fertility, gestation, viability of pups, or maternal lactation. Feeding carbaryl at doses up to 500 mg/kg/day in the diet did not increase the incidence of teratogenic anomalies or have an effect on fertility or gestation (Weil et al., 1972). Carbaryl fed to pregnant beagles at dietary doses of 0, 3.125, 6.25, 12.5, 25, and 50 mg/kg/day resulted in terata in 9 to 18 percent of the pups born to animals receiving the 4 highest doses. One-half of the dams in each carbaryl treated group had dystocia (difficulty at the time of delivery) due to uterine atony. There were no cases of dystocia in the controls (Smalley et al., 1968). Positive examples of developmental toxicity are seen in several other species, however, adverse effects occur only at dose levels which produce toxicity in the maternal animals (Robens, 1969; Weil et al. 1973; Collins et al., 1971).

Daily oral doses of 2 and 20 mg/kg of carbaryl in the monkey (Macacca mulata) caused an increase in the number of spontaneous abortions (Dougherty et at., 1971).

Carcinogenic Potential: Mice given carbaryl daily, by gavage tube, at the maximum tolerated dose for 18 months did not have a significant increase in tumors compared to a control group (Innes et al., 1969). Other reports are inconclusive. Total evidence to date has not established a carcinogenic potential for carbaryl. Should any such potential surface, there would be a limited impact based on extensive negative findings which have been previously established.

Mutagenic Potential: Carbaryl has been found to be a weak mutagen in bacterial assays (Cook et al., 1977) and mammalian cell culture (Ahmed et al., 1977). Exposure of virally transformed human cells (VA-4) in culture to carbaryl initiates unscheduled DNA synthesis at exposure concentrations as low as 1 uM (Ahmed et al., 1977).

Semen samples were analysed from 50 carbaryl production workers who spent one year on the job. A significant elevation of sperm abnormalities was seen in the currently exposed workers as compared to controls, however, a cause and effect relationship was not established (Wyrobek et al., 1980).

Exposure Potential

For control of gypsy moth, an application rate of one pound of carbaryl per acre is indicated on existing labeling. At this application rate, the concentration of carbaryl expected to reach the ground under ideal conditions would be 14 micrograms/cm^2.

DIFLUBENZURON
(DIMILIN)

Background

Dimilin is the trade name for diflubenzuron (N-[([4-chlorophenyl]amino) carbonyl]2,6-difluorobenzamide). Diflubenzuron (DFB) acts as an insect growth regulator by interfering with the deposition of insect chitin (Marx, 1977). It is a white, sparingly soluable, crystalline solid with a melting point of 230°C. It is marketed in both granular (Dimilin-1G) and wettable powder (Dimilin W-25) forms. It has been registered by the EPA for use to control gypsy moth in forested areas (Anon., 1981).

Toxic Potency

A. Single Dose LD_{50} (Willcox et al., 1978; CDFA #377-012)

1. Oral

a. mouse	4,640 mg/kg (tech)
b. mouse	10,000 mg/kg (W-25)
c. rat	4,640 mg/kg (tech)
d. duck	5,000 mg/kg (tech)
e. bobwhite quail	5,000 mg/kg (tech)
f. rat	10,000 mg/kg (W-25)

2. Dermal

a. rabbit	20,000 mg/kg (50% Kaolin)
b. rabbit	4,640 mg/kg (W-25)
c. rabbit	4 ml/kg (50% paste)

3. Inhalation

a. rat	No effect at 35 mg/l for 6 hrs
b. rat	No effect at 50 mg/l for 6 hrs
c. rabbit	No effect at 30 mg/l for 6 hrs

4. Intraperitoneal

a. mouse	2,150 mg/kg (tech)

B. 96-hour HC_{50}

1.	Bluegill sunfish	135 ppm (tech)
2.	Bluegill sunfish	660 ppm (W-25)
3.	Channel catfish	500 ppm (W-25)
4.	Rainbow trout	240 ppm (W-25)
5.	Fathead minnow	180 ppm (W-25)
6.	Water flea	1.5 ppb (W-25) 48 hrs.
7.	Snail	125 ppm

C. Multiple Doses

1. No observable effect

In an experiment to determine the toxic effects of DFB fed to mice, a no-effect level was established as 12.5 ppm in the diet (CDFA #377-012).

2. Feeding experiments

DFB has been fed to animals at concentrations ranging from 10 to 100,000 ppm in the diet. Foci of liver cell necrosis were seen in some mice fed 50 ppm for 6 weeks (CDFA #337-025). DFB feeding caused cyanosis in mice fed >200 ppm (Willcox et al., 1978; Bentley et al., 1979; CDFA #377-025). This cyanosis was caused by sulfhemoglobin. There was no depression of glycosaminoglycan synthesis (Bentley et al., 1979). Cattle fed up to 18 mg/kg/day showed no ill effects (Miller et al., 1976; Ivie, 1978; Miller et al., 1979). Only .02 ppm DFB appearing in the milk of treated animals. Swine and sheep also showed no apparent illnesses as a result of DFB feeding. Dogs showed no morphological abnormalities which could be attributed to the feeding of DFB (CDFA #377-013). Chickens fed DFB up to 250 ppm in the diet showed a trend to higher body weights, but no other significant differences were found (Miller et al., 1976; Kubena, 1981). In a separate test, DFB caused a dose related decrease in testosterone levels of male chicks. This caused a retardation of sexual development. Hens showed an increase in fat deposition (Smally, 1976).

3. Non-target Impact

a. Invertebrates

DFB is acutly and chronically toxic to small estuarine crustaceans (Mulla et al., 1975; Christiansen et al., 1978; Farlow et al., 1978; Forward et al., 1978; Julin et al., 1978; Nimmo, 1979; Nimmo et al., 1980). Acceleration of the molt cycle has been observed in several species of crustaceans (Gulka et al., 1980). The effect of DFB on residential-recreational lakes can be dramatic. Certain invertebrates are totally eliminated for long periods of time following the application of DFB (Apperson et al., 1978; Ali et al., 1978; Ali et al., 1980).

b. Fish

Sublethal exposure (10 mg/L) caused a drop in glutamate oxalacetate transaminase (GOT) serum values in rainbow trout. No other effect was noted (Madder et al., 1978). Trout and salmon exposed to 1gm/L for 15 minutes showed no mortality (McKague et al., 1978). At 0.2 ppm, DFB caused hyperactivity in mosquito fish. The hyperactivity diminished to normal by day 14 (Ellgaard et al., 1979). Atlantic salmon (parr) tend to avoid Dimilin-1G and its blank carrier, Florex, when given a choice of flumes to enter (Graner et al., 1978).

Biokinetics

A. Biological Half Life

In rats, excretion was almost complete after 72 hours (Willems et al., 1980).

B. Metabolic Products

Metabolic products include 4-chloroaniline, 2,6-diflurorobenzoic acid, 4 chlorophenylurea, 4-chloroacetanilide, acetanilide, and 4-chlorophenol (CDFA #377-003 and #377-027; Seuferer et al., 1979).

C. Excretion

Metabolic studies in rats and bovines have shown that DFB is largly excreted through the feces. Bile excretion is the major route of metabolite excretion. In cows, it was discovered that 85 percent of administered the DFB is eliminated in the feces, while 15 percent is excreted in urine (Ivie et al., 1978). No repiratory excretion of DFB was found in the rat (Willems et al., 1980). DFB is rapidly metabolized by soil microorganisms (Seuferer et al., 1979).

D. Storage Potential

In a bioaccumulation test, DFB did not exhibit a strong tendancy to bioaccumulate (Metcalf et al., 1975). It concentrated less than methoxychlor, but slightly more than malathion or terbufos (Belluck et al., 1981). Fish eliminate DFB rapidly and there is no partition of the metabolite p-chlorophenylurea in the gills. Fish bioaccumulate DFB by a factor of as much as 80 compared with aquatic concentrations (Schaefer at al., 1979). A crawfish exposure experiment showed that this species does not bioaccumulate DFB (CDFA #377-003).

Specific Toxicity

A. Reproductive/Teratogenic Effects

DFB did not cause teratogenic effects in developing mice and did not pass through embryonic membranes, nor was it passed to suckling mice (CDFA #377-026). In swine, sheep and rabbits, no changes in

litter size, fetal loss or incidence of major malformations were found (Escobar et al., 1980). Mouse litters did show a transient, but nonsignificant increase in litter weight. No loss of libido was found in bulls fed DFB (Miller et al., 1979). The administration of DFB to mice resulted in no increase in the incidence of dominant lethal mutations (CDFA #377-025).

B. Carcinogenic Potential

Carcinogenicity data have been inconclusive. Additional cancer tests are being instigated by the registrant at the request of EPA (Anon., 1978).

C. Mutagenic Potential

The results of several tests indicate that DFB and its metabolites are not very mutagenic (CDFA #377-025, #377-023, #377-026; Macgregor et al., 1979). Only 4-chloroaniline gives a weak mutaginic response. Further testing will be necessary (CDFA #377-025).

Exposure Potential

A. Use Pattern

Dimilin is approved by EPA for use against gypsy moth. It has been used in forested areas as part of a control and eradication effort.

B. Application Rates - Frequency

The label application rate is given as 2 to 4 oz. per ha. This converts to 0.7 ug/cm^2. The label also indicates one application per season.

C. Environmental Degradation

DFB shows a fair amount of persistance on cotton leaves, with detectible residues still available after 4 weeks. It is not photodegraded. Heavy rainfall can causes appreciable reduction of residues (Bull et al., 1978; Mansager et al., 1979). In water, DFB has a variable decay rate relative to the pH and temperature. Warm, akaline water cause the most rapid degradation (Ivie et al., 1980). In water pools, adsorbtion is the most likely pathway of DFB loss (Schaefer et al., 1976).

DYLOX

Background

Dylox (O,O-dimethyl-2,2,2-trichloro-1-hydroxy-ethylphosphonate) is an organophosphate chemical used as an insecticide and, as a drug to combat schistosomes in livestock and humans. It was introduced as an insecticide in 1952 and as a medication in 1960.

Toxic Potency

The following acute oral LD_{50}'s have been determined: Mice 788-822 mg/kg (Yamashita, 1960), rats 450 mg/kg (Dubois et al., 1955). Intraperitoneal LD_{50}'s are: for mice, 500-523 mg/kg (Yamashita, 1960; Dubois et al., 1955); for rats, 190-250 mg/kg (Brodeur et al., 1963); and, for guinea pigs, 300 mg/kg (Dubois et al., 1955). The dermal LD_{50} in rats is >2,000 mg/kg, and the inhalation LC_{50} for rats is 1,300 ug/m^3 (Registry of Toxic, etc., 1979).

Biokinetics

There is experimental evidence that Dylox does not affect acetylcholinesterase directly, but is first convented nonenzymatically to D.D.V.P. (Nordgren et al., 1978) (O,O-dimethyl-2,2-di-chlorovinyl phosphate), which then acts as the enzyme inhibitor (Reiner et al., 1974; Holmstedt et al., 1978). The disappearance of Dylox and its metabolites from serum after injection into mammals, has been shown to be exporential from 10 minutes to 6 hours after injection, with a half-life of 2 hours and 20 minutes Holmstedt et al., 1978). Seventy percent of the metabolized products are excreted in the urine within 16 hours (Bull. et al., 1969).

SPECIFIC TOXICITY

Mutagenicity: Dylox has been found to be a mutagen in several bacteriological studies in vitro and in vivo. In vitro (Simmon, 1979; Batzinger, et al., 1976; Hanna et al., 1975) it has been found to be mutagenic with or without S-9 microsomal extracts. In vivo (Batzinger et al., 1976) Dylox has been found to be mutagenic to test bacteria which are injected intraperitoneally into mice treated with Dylox.

Teratogenicity and Fetotoxic Affects: Dylox was found to be fetotoxic and teratogenic when given by gavage to rats, hamsters, and mice (Staples et al, 1979; Staples et al., 1976). It was also fetotoxic and teratogenic when given orally to rats (Staples et al., 1976; Mantson et al., 1976). Dylox is suspected of causing brain damage in piglets born to sows treated with Dylox during pregnancy (Bolske et al., 1978; Kronevi et al., 1975).

Oncongenicity: Several studies have been conducted to evaluate the oncogenic potential of Dylox. It has been reported to be nontumorogenic in some studies (Teichmann et al., 1978 a,b,c; Blair et al., 1976), while other studies have found a higher incidence of carcinogenic tumors than controls (Gibel et al., 1971; Gibel et al., 1973).

Neurotoxicity: Dylox has been found to be a delayed neurotoxin in hens (Olajos et al., 1979) and rats (Finkiewicz-Munawiejska et al., 1978). Delayed neurological disorders have also been recorded following several human poisonings with Dylox (Kazakevich et al., 1972; Bidstrup et al., 1953; Hierons et al., 1978).

Exposure Potential

Dylox decreased from a concentration of 105 ppm in clover after a field application to a concentration of 2 ppm after 7 days; and in the laboratory, Dylox was found to have a half life of 8 hours in water at a pH of 6.9 (Gilpatrick et al., 1967). The label application rate of Dylox for gypsy moth is 851 grams/ acre which converts to 21.03 ug/cm^2 of active ingredient.

Kryocide

Background

Kryocide is a micron size grade of cryolite produce by Pennwalt. Cryolite is a mineral, chemically known as sodium fluoaluminate and contains approximately 49 percent fluorine.

The first commercial use of Kryocide was in 1932-1933 when the Department of Agriculture found cryolite to be a satisfactory substitute for arsenicals for the control of codling moth on apples, work having begun on this application in 1926.

Toxic Potency

The oral LD_{50} of cryolite in the rat has been reported to be 200 mg/kg (Merek, 1976). The dietary LD_{50} for rats fed orally was greater than 10,000 mg/kg in the diet. The 48-hour LC_{50} for rainbow trout exposed to cryolite was 47,000 ppb (CDFA).

In a two-month study, young rabbits were 1,000, 2,000, or 4,000 ppm of cryolite in the diet. This resulted in varying degrees of loss in appetite, weight, or growth rate in the treated rabbits. Fatalities occurred within 7 days at the highest concentration (CDFA).

The minimum lethal dose (MLD) in mg/kg of body weight in rabbits is reported as >6,000 mg/kg and >500 mg/kg in dogs (CDFA).

SPECIFIC TOXICITY

Mutagenic Activity: Female rats exposed six hours daily for five months to cryolite by inhalation at a concentration of 3 mg/m^3 resulted in an increase in the percentage of aberrant cells in the bone marrow (Guleva et al., 1972).

No other information dealing with the biological effects of cryolite has been located at this time.

Exposure Potential

For gypsy moth, the maximum suggested application rate of 50 pounds Kryocide (96% cryolite) per acre would result in a distribution of 538 micrograms/cm^2.

METHOXYCHLOR

Background

Methoxychlor is a chlorinated hydrocarbon which was first synthesized in 1893. Its insecticidal properties were not discovered until 1944. The EPA has approved the use of methoxychlor as an insecticide on several agricultural crops, beef and dairy cattle, goats, sheep, swine, and for spray treatments of grain bins, mushroom houses, and other agricultural premises (IARC, 1974).

Toxic Potency

The oral LD_{50} of methoxychlor in the rat has been reported to be 6,000 mg/kg (Merck, 1976). Rats fed 100 and 500 ppm methoxychlor in the diet for 18 weeks showed some growth retardation but were otherwise without symptoms (Kunze et al., 1950). Rats fed 0.16 percent methoxychlor in the diet also showed growth suppression, but no histological changes or decrease in life span were noted (Hodge et al., 1952). Dogs fed 300 mg/kg/day for 1 year showed no evidence of tissue damage (Hodge et al., 1952), while dogs ingesting 4,000 mg/kg/day for 24 weeks experienced convulsions and tissue damage (Tegeris et al., 1966).

Methoxychlor is slightly irritating to human skin but has a low absorption potential. The estimated human fatal oral dose is 7,500 mg/kg. Continued ingestion over long periods of time may cause kidney damage (Merck, 1976). Acceptable daily intake in man has been reported to be 0 - 0.10 mg/kg/day (IARC, 1974).

Biokinetics

In a study on mice, 98.3 percent of orally ingested methoxychlor was eliminated after 24 hours (Kapoor et al., 1970). Ninety-six percent was eliminated unchanged; metabolites were identified as 2-(p-hydroxyphenyl)-2-(p-methoxyphenyl)-1,1,1-trichloroethane and 2,2-bis(p-hydroxyphenyl)-1,1,1-trichloroethane (Menzie, 1974). Another mouse study showed that 90 percent of excreted methoxychlor was in the feces and 10 percent was in the urine (Kapoor et al., 1970). Rats fed 100 and 500 ppm methoxychlor in the diet for 18 weeks stored 1 to 7 ppm and 14 to 36 ppm methoxychlor in the fat, respectively (Kunze et al., 1950). No methoxychlor was detected in the fat at either dose level 2 weeks after the feeding was discontinued.

Specific Toxicity

Methoxychlor has been found to decrease the action of estrogens in the uterus of several species [Welch et al., 1968; Cecil et al., 1975; Bulger et al., 1978(a)(b)]. Doses of 2,500 and 5,000 ppm in the diets affected reproduction in adult rats and also affected reproduction of the young in the next generation (Harris et al., 1974). Dams given methoxychlor via gastric intubation during days 6 through 15 of gestation showed fetotoxic effects at 200 and 400 mg/kg; wavy ribs were produced at 100 mg/kg (Khera, 1978).

Carcinogenicity studies performed on rats and mice by the National Cancer Institute showed no significant increase in the incidence of tumors (NCI, 1978). Other studies have given similar results (IARC, 1974).

No published reports of mutagenic testing of pure methoxychlor have been located at this time. An Ames assay of methoxychlor impurities showed only slight mutagenic effects of one impurity on one experimental strain (Grant et al., 1976). An intraperitoneal injection of 30 mg/kg of a methoxychlor, dimethoate, and malathion mixture in male mice showed no evidence of mutagenicity in a dominant lethal assay (Degraeve et al., 1977).

Exposure Potential

For control of the gypsy moth, a maximum application rate of 7.5 pounds active ingredient per acre of methoxychlor is given on product labels. At this rate, the concentration of methoxychlor expected to reach the ground under ideal conditions would be 84.1 micrograms/cm^2.

SUMMARY

Evaluation of these agents will continue. Any decision rendered with respect to use of any individual agent will be based of the total information available with respect to any adverse health potential.

INSECT HORMONE

In addition to potential pest control through direct intoxication, use of a synthetic hormone to disrupt mating of adults moths is also possible. The following information has been identified with respect to potential toxicity of the hormone product.

DISPARLURE

Background

The scientific name for disparlure is cis-7,8-epoxy-2-methyloctadecane. The compound is an artificial pheromone developed by Herculite Products for use in Federal and State programs to trap male gypsy moths in scouting operations. It has been used for suppression and eradication operations by the USDA including aerial applications over residential areas in Maryland.

Two formulations are EPA registered: Luretape, for ground applications and, Disrupt, for aerial applications. Neither product is registered in California at this time.

Toxic Potency

The single dose LD_{50}'s of this compound are relatively high. The oral LD_{50} is 34,600 mg/kg. The dermal LD_{50} is 2,025 mg/kg. The material is

classed as a nonirritant from an eye study performed on albino rabbits (score 12.0/110).

Specific Toxicity

No studies have been identified which assess specific toxicities for this material. The registration on ornamental trees does not require a residue tolerance. No food crop uses are registered.

Exposure Potential

One ground application per season with Luretape is recommended at 1.8 grams a.i. per acre. One aerial application per season with Disrupt is recommended at 4-8 grams active ingredient per acre.

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February 19, 1982

CARBARYL DATA BY SUBJECT AND AUTHORS

Acute Toxicity

Serrone, et al., 1966
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Singh, 1973
Chaiyarach, et al., 1975
Statham, et al., 1975, 1976
Bahl, et al., 1978
Pipy, et al., 1979
Mount, et al., 1981

Subacute Toxicity

Desi, et al., 1974
Dikshith, et al., 1976
Neskovic, 1979
Neskovic, et al., 1979

Inhalation Toxicity

Nye, et al., 1976

Chronic Toxicity

Knaak, et al., 1965, 1967(a)(b), 1968
Leeling, et al., 1966
Nir, et al., 1966
Ghadiri, et al., 1967
Baron, 1968
Shtenberg, et al., 1968
Vashakidze, 1968
Pavlova, 1969
Smalley; et al., 1969
Bend, et al., 1971
Hassan, et al., 1971
Andrawes, 1972
Boyd, 1972
Santolucito, 1972
Elespuru, et al., 1973
Shah, et al., 1973
Thomas, et al., 1973
Cecil, et al., 1974
Chin, et al., 1974, 1979
Dieringer, et al., 1974
Hwang, et al., 1974
Eisenbrand, et al., 1975, 1976
Jordan, et al., 1975
Mirvish, 1975
Pomeroy, et al., 1975
Street, et al., 1975
Ahdaya, 1976
Egert, et al., 1976
Khera, 1976
Kitagawa, et al., 1977
Bursian, et al., 1978, 1979
Abou-Donia, 1979
Anger, et al., 1979
Benard, et al., 1979
Quarles, et al., 1979
Beraud, et al., 1980

Reproductive Effects/ Teratogenicity

Carpenter, et al., 1961
Marliac, 1964
Ghadiri, et al., 1966
Khera, et al., 1966
Smalley, et al., 1968
Vashakidze, 1968
Robens, 1969
Courtney, et al., 1970
Collins, et al., 1971
Dougherty, et al., 1971
Hassan, 1971
Weil, et al., 1972, 1973
De Norscia, et al., 1973
Earl, et al., 1973(a)(b)
Lillie, 1973
Golbs, et al., 1974
Thomas, et al., 1974
Weis, et al., 1974
De Rosa, et al., 1976
Graf, et al., 1976
Proctor, et al., 1976
Khera, 1976
Strother, et al., 1976
Weis, et al., 1976
Bursian, et al., 1977, 1979
Declume, et al., 1977, 1979
Moscioni, et al., 1977
Murray, et al., 1979
Quarles, et al., 1979
Seifert, et al., 1979
Solomon, et al., 1979
Sternberg, 1979
Cambon, et al., 1980
Eto, et al., 1980
Strother, et al., 1980
Wyrobek, et al., 1981

Mutagenicity

Ashwood-Smith, et al., 1972
Brzheskii, 1972
Epstein, et al., 1972
Hoque, 1972
Elespuru, et al., 1974
Siebert, et al., 1974
Mc Cann, et al., 1975
Marshall, et al., 1976
Beniqui, et al., 1979
Rani, et al., 1980
Wojciechowski, et al., 1980

Oncogenicity

Innes, et al., 1969
Shimkin, et al., 1969
Eisenbrand, et al., 1975
Walker, et al., 1975
Eisenbrand, et al., 1976
Lijinsky, et al., 1976
Preussmann, et al., 1976
Sternberg, 1979

Human Exposure

Best, et al., 1962
Jegier, 1964
Knaak, et al., 1967(b)
Wills, et al., 1968
Farago, 1969
Maibach, et al., 1971
Chin, et al., 1974, 1979
Feldmann, et al., 1974
Tannenbaum, et al., 1974
Comer, et al., 1975
IARC, 1976
Regan, et al., 1976
Spiegelhalder, et al., 1976
Wyrobek, et al., 1981

Environmental/
Zoological Effects

Amer, 1964, 1965
Georghiou, et al., 1964
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Amer, et al., 1968
Lamberton, et al., 1970
Aly, et al., 1971
Carlson, 1971
Eichelberger, et al., 1971
Karpel, 1973
Korn, 1973
Wauchope, et al., 1973
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Summary Articles

Dolinger, et al.
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March 3, 1982

SUPPLEMENTAL HEALTH HAZARD ANALYSIS OF CHEMICALS DISCUSSED IN THE DRAFT ENVIRONMENTAL IMPACT REPORT FOR THE GYPSY MOTH ERADICATION PROJECT, COUNTY OF SANTA BARBARA, JANUARY 26, 1982

METHOXYCHLOR AND KRYOCIDE

Extensive review of data concerning each of the six candidate chemicals mentioned in the draft Environmental Impact Report (EIR) has been conducted. Both methoxychlor and kryocide were not considered as the chemicals of choice for an eradication program. Either of these chemicals would require the heaviest doses to be applied to the environment of all the chemicals proposed. While much is known about these chemicals there are still significant data gaps. Both of these agents have been in use as pesticides for many years, but have, so far, escaped some of the requirements for data development currently applied to chemicals to be used as pesticides. It is suggested that these chemicals not be considered for use in this project.

DYLOX

Dylox has been associated with a variety of potential effects to living systems including mutagenicity, teratogenicity, fetotoxic effects, neurotoxicity and oncogenicity. The producer of Dylox points out that the majority of studies in which adverse events are reported are from the European and Communist Block countries. It is suggested that the formulations used in those tests do not meet the same standards required in the United States. These comments, however, are not adequate assurance that the potential for these effects has been adequately studied in formulations manufactured in the United States, and are, therefore, not a cause for continued concern. It is therefore recommended that Dylox not be considered for use in areas that are inhabited by humans.

ACEPHATE

Acephate has been associated with some degree of mutagenic activity. Original toxicology studies with acephate were questioned on the basis of inadequate documentation of proper laboratory procedure. Many of these studies had to be repeated. Reanalysis of original data, as well as consideration of newly developed data, is now nearing completion. Verbal communication with Chevron Chemical Company indicates that repeat studies were done and have shown no immediate or long-term health hazards associated with proper use of acephate based on observations in studies on laboratory animals. Final submission of this data to regulatory agencies is not yet complete. Acephate may be a viable chemical for use in populated regions once data review has been completed, if no significant hazards are identified. (Acephate is currently available for use around yards and gardens in California). Until then, the prudent course would be to avoid extensive use of this chemical in populated areas, while still recognizing potential for use in the future.

DIFLUBENZURON

Diflubenzuron is perhaps the least potent agent under consideration with respect to acute toxic effects in mammals. The exposure potential is also the least with this agent, in that the rate of application is the lowest of all the chemicals under consideration. The material does not accumulate in biological tissues and is readily excreted. There were no adverse effects on reproduction or any indication of teratogenic effects with administration of diflubenzuron to laboratory animals. A weak mutagenic potential was seen in several studies, however, the majority of studies show no mutagenic activity.

The main concern regarding diflubenzuron centers around studies done with rodents in which an excessive number of lymphomas appeared with prolonged administration. The interpretation of these studies has been challenged. It is generally agreed that these studies are not conclusive, however, various flaws in study design and conduct were identified. New studies of proper design were initiated in the summer of 1981 to resolve the conflicts generated by the previous studies. These new studies will not be completed until 1983 with final reports not likely to be ready until sometime in 1984. The use of diflubenzuron over populated areas should, therefore, be avoided until resolution of the existing conflict regarding carcinogenic potential is complete. Use in nonpopulated areas could be considered.

CARBARYL

Carbaryl is perhaps the most studied of all the chemicals reviewed for use in Gypsy Moth eradication. From the standpoint of immediate toxicity the potency of carbaryl is intermediate in comparison with other chemicals used as pesticides. Human exposure studies have shown, however, that moderate exposure is not necessarily associated with acute toxic symptoms. Carbaryl does not accumulate in body tissues and is readily excreted with a half life of less than 24 hours. Weak mutagenic activity has been reported in several isolated studies in which carbaryl has been tested. The majority of tests for mutagenic activity, however, are negative. Carbaryl is not considered to be mutagenic other than in the specific tests where the weak activity was observed.

Three areas of concern have been identified with respect to potential health risks with the use of carbaryl. Studies done *in vitro* with cultured human embryonic lung tissue cells showed an increased viral penetration with certain viruses and not with others when carbaryl is added to the culture medium. There is no known correlation with such findings and *in vivo* sensitivities. No increased incidence of infection has been reported from groups, such as employees handling carbaryl in its manufacturing and formulation, with observations being made over periods as long as ten years.

Carbaryl can be nitrosated producing nitrosocarbaryl. The potential for this reaction to this occur in the stomach of animals ingesting carbaryl and an appropriate nitrosating agent has been demonstrated. This compound is not found, however, in routine metabolism studies of carbaryl. This theoretical consideration is no different than that with many other

compounds which occur in the normal environment. Nitroso compounds are notoriously capable of producing mutagenesis and carcinogensis when administered in concentrated amounts to laboratory animals. Nitroso-carbaryl also has these characteristics.

The greatest concern over carbaryl toxicity has come from studies of teratogenesis and reproductive interferance. Malformed offspring have been born to laboratory animals given acutely toxic doses of carbaryl during their pregnancy. Lower doses do not produce such effects. Doses in these studies are generally given daily over a prolonged period of time. One study, conducted in dogs, suggests some teratogenic capability for carbaryl. In this study, 38 litters were born to mothers treated with carbaryl at doses ranging from 3.125 milligrams per kilogram of body weight to 50 milligrams per kilogram of body weight. One hundred and eighty-one pups were born, of which 21 showed some developmental abnormality. Only one of seven pups born to two mothers given the highest dose had abnormalities. The remaining abnormalities were seen in pups from seven litters, the highest incidence occurring in animals given 12.5 milligrams of carbaryl per kilogram of body weight. The incidence of these abnormalities is therefore not strictly dose associated. The abnormalities seen represent, primarily, a failure to develop rather than an alteration in development leading to malformation. All of the female dogs showed signs of acute toxicity at the time of delivery of their litters. Dosing was carried out daily over the entire period of gestation with significant toxicity to the pregnant animal. Reviewers have pointed out that the movement and implantation of ova in dogs differs from other mammalian reproductive systems, including humans. It is also pointed out that dogs do not generally hydroxylate compounds such as carbaryl and that hydroxylation is a primary reaction in metabolism of carbaryl in most other species, including man.

An extensive review of carbaryl toxicity was conducted by the United States Environmental Protection Agency (EPA). In their final position document released in December 1980, it was concluded that the extensive data base reviewed did not justify specific regulatory action against carbaryl at that juncture.

In view of the extensive amount of study which has taken place with carbaryl in over 20 years of very heavy use in the public sector without identification of any associated health abnormalities, and the lack of correlation of the findings in dogs with respect to fetotoxicity, the proposed dose of carbaryl for Gypsy Moth eradication programs, from either ground or aerial application, has not been associated with specific hazards to public health or significant risk of either immediate or delayed toxic effects. It is therefore recommended that, in populated areas, chemical application be limited to the use of carbaryl at the recommended labeled dosages.

Seven volumes of selected literature references have been prepared in conjunction with the review conducted by the California Department of Food and Agriculture (CDFA) with respect to potential health hazards from the use of carbaryl. The EIR is not a comprehensive "cite all" document, but rather a summary of available information. A complete bibliography of the seven volumes of literature on carbaryl compiled by CDFA is appended for reference.

Several product formulas which incorporate carbaryl as the active ingredient have been reviewed as possible candidates for use in a Gypsy Moth eradication program. Some of these formulas include formaldehyde in low concentrations as an insecticidally inert ingredient. The use of these products is not recommended in view of recent published information indicating that formaldehyde is associated with an increased incidence of malignant tumors in animals exposed via inhalation. A review of the inert ingredients in SEVIN Sprayable, SEVIN-4 Oil, and SEVIN-50 WP has been conducted by CDFA. While product formulation falls under trade secret protection and cannot be specifically revealed, a review conducted by CDFA has resulted in the conclusion that the above-named products of Union Carbide Corporation do not contain toxicologically hazardous materials and could be considered for use in a Gypsy Moth eradication program.

Individuals expressing concern regarding specifics relative to the analysis of toxicity for carbaryl, including its mutagenic potential, carcinogenic potential, teratogenic potential, potential for allergic reactions and toxicity of breakdown products and products of metabolism are referred to the seven volumes of literature submitted to the County Agricultural Commissioner of Santa Barbara along with the summaries which were submitted for preparation of the Environmental Impact Report.

1220 N Street
Sacramento
95814

March 3, 1982

Lawrence Hart, M.D., M.P.H.
County of Santa Barbara
Health Care Services
300 San Antonio Road
Santa Barbara, California 93110

Dear Dr. Hart

Mr. Graydon Hall, Agricultural Commissioner for the County of Santa Barbara, asked me to comment on the concerns expressed in your memo of February 25, 1982. As you noted, an extensive volume of materials has been prepared with respect to the toxicological assessment of each of the chemicals mentioned in the draft EIR for possible employment in a gypsy moth eradication program. These materials are available through Mr. Hall's office for independent public health risk analysis by any groups or individuals interested in making such an assessment.

After reviewing each of the chemicals mentioned in the draft Environmental Impact Report, I have recommended to Mr. Hall that diflubenzuron (Dimilin) and acephate (Orthene) not be used in residential areas at this time. Further assessment of the toxicity of these chemicals is necessary before a reasonable degree of confidence can be reached with respect to lack of potential adverse health effects on humans. Certain data are missing with respect to acephate while data on diflubenzuron have suggested a possible association with lymphoma formation in laboratory animals fed diflubenzuron for prolonged periods of time. Studies on acephate are reported to now be complete, however, review of the information has not yet taken place. As for diflubenzuron, life-time feeding studies in rodents were initiated in summer of 1981 and will not be complete until sometime in 1984 in all likelihood. The use of diflubenzuron or acephate could be considered for nonpopulated areas.

The use of Dylox is not a consideration inasmuch as numerous studies have associated this chemical with adverse effects, including teratogenicity, mutagenicity, carcinogenicity, and neurotoxicity. Methoxychlor and kryocide are not particularly efficacious and have many data gaps associated with them since they came into use several years prior to the stringent data requirements now in effect.

The only chemical available then, for consideration for use in populated areas, is carbaryl (Sevin). The United States Environmental Protection Agency (EPA) recently completed a review of carbaryl data with respect to potential health hazards and issued a final decision document in December 1980. In this document, the EPA notes that the data base available for carbaryl is more extensive than ordinarily available. From the standpoint of lethal potency, carbaryl is categorized as moderately toxic. Moderate doses of carbaryl are necessary to initiate acute symptoms of intoxication. Use of carbaryl in the gypsy moth program would require approximately one pound of active ingredient per acre applied by air and, while such precise dosage is not possible for ground applications, similar concentrations could be anticipated to be distributed from the ground although not as uniformly as an aerial application (i.e., "hot" and "cold" spots). Worker exposures to carbaryl have been discussed in the literature showing no adverse health effects after prolonged exposures to relatively high environmental concentrations of carbaryl. Carbaryl does not accumulate in the body and is readily excreted with a biological half-life of less than 24 hours.

Carbaryl is not considered to be a mutagen or a carcinogen based on existing information. It is, therefore, not possible to calculate a statistical probability of the occurence of these events as a response to public exposure to carbaryl. The same is true with respect to allergic reactions. Carbaryl is not known to be a specific allergenic stimulant and any such reactions would be host-specific. Any statistical probability of such occurrences being seen would have to be based on population characteristics, not on the chemical characteristics of carbaryl. In a joint FAO/WHO review of carbamate and organophosphate pesticides used in agriculture with respect to public health (VETTORAZZI, 1976) 50 known cases of illness associated with carbaryl exposures are discussed in which no fatalities are reported. Three of these exposures were in children with accidental ingestion. Thus, very few cases of intoxication have been observed during the more than 20 years of extensive use of carbaryl.

I've enclosed a supplemental health hazard analysis document, which was submitted to Mr. Hall, which discusses the various potential hazards with respect to health risks of each of the chemicals mentioned in the EIR. The teratogenic risk of carbaryl is discussed in that document; available data do not lend themselves to a statistical calculation of probability for the occurrence of this event. Dosing of the laboratory animals took place over a continuous time period during gestation with "no observable effect levels" also detected. Teratogenic response is not generally viewed the same as carcinogenic responsiveness. Carcinogenic action of chemicals is considered to represent a risk at all dosages; the statistical formulas applied to this carcinogenic probability are not appropriate when the effect is teratogenesis. A risk assessment of teratogenicity, therefore,

is limited to a qualitative assessment rather than a calculation of statistical probability.

While in Santa Barbara on February 24th and 25th, I met Mr. Ben Gale, Director of Environmental Health Services from your agency. We met with a committee of physicians of the Santa Barbara County Medical Society to discuss the issues raised in your memo relative to implementation of planning for improved community awareness; monitoring of air, water, food, etc.; developing a response plan in the event of accidents, such as aircraft emergencies or ground spills; and plans for health monitoring programs for the community. These items do not necessarily belong in the environmental impact report, however, they are essential to community planning with respect to the actual physical conduct of any activities wherein unscheduled (accidental) events may result in additional hazards if not properly handled. I have suggested to Mr. Hall that a committee of health experts from the Santa Barbara community be established to assist in such planning. I have made myself available to the Medical Society to serve as a liaison to the committee for the purpose of supplying information they may require. I recommend that a representative from the county health agency be a liaison member of that committee and also someone from the State Department of Health Services. Much of the planning required will be the same, irrespective of the specific agent(s) to be used in any community pest management program.

I agree that extreme caution and thorough analysis should precede any widespread application of chemicals into the environment, regardless of where that environment exists. I am available to you for specific consultation on any matters relative to the use of chemicals in pest management and particularly as it relates to the gypsy moth problem in the Santa Barbara area. I look forward to hearing from you and working with members of your staff in the development of a community program appropriate to whatever activity may take place in your area involving the use of pesticide chemicals.

Sincerely

P. H. Kurtz, M.D., Ph.D.
Medical Coordinator
Worker Health and Safety Unit
(916) 445-5474

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State of California

Memorandum

To : Lori Johnston, Acting Assistant Director
Pesticide Management Environmental Protection
and Worker Safety

Date : March 1, 1982

Place : Sacramento

From : **Department of Food and Agriculture** – Keith T. Maddy, Unit Chief/Staff Toxicologist
Worker Health and Safety Unit

Subject: Summary of Toxicological Data on Bacillus Thuringiensis

There is consideration being given to using Bacillus thuringiensis (B.t.) in populated areas of Santa Barbara County as a part of a Gypsy Moth Eradication Program. Below is summarized toxicology data on the HD-1 strain of this organism.

Bacillus thuringiensis (B.t.) is a bacterium which already occurs naturally in the environment. B.t. has a highly specific mode of action. It effectively controls caterpillar larvae; however, the HD-1 strain of B.t. is not toxic to mammals, fish or other wildlife at recommended field rates. This is supported by a full toxicologic evaluation by registrants and extensive testing by independent scientists. Further, in over 10 years of commercial use, no reports of adverse effects to the environment have been documented. Unlike most chemical pesticides, B.t. is ideally suited for use in integrated pest management programs since the active ingredient does not interrupt activities of beneficial insects.

ORAL TOXICITY

No toxicity in mice, rats or dogs has been demonstrated with single dosages up to 10,000 mg/kg of body weight.

Thirteen-week dietary administration of technical material to rats at dosages of 8,400 mg/kg produced no toxic effects.

Two-year chronic dietary administration of technical material to rats at 8,400 mg/kg produced no tumorigenic or oncogenic effects.

INHALATION TOXICITY

No toxic effects were observed in rats when B.t. was instilled directly into the lungs at rates up to 5 mg/kg of body weight. This translates to a value 10,000 times greater than a bystander could expect during spray programs. Humans exposed daily to B.t. spores for over 10 years as production workers have shown no adverse effects.

DERMAL TOXICITY

Mild, transient dermal involvement was demonstrated, but no systemic toxicity was noted in rabbits when a formulation containing B.t. was applied to abraded skin at 1 mg/kg/day for 21 days. In other studies, no LD_{50} could be determined in rabbits with single dosages of up to 3,400 mg/kg of body weight.

EYE IRRITATION

No corneal opacity was observed in rabbits treated with 0.1 ml of a formulation of B.t. Only mild, transient irritation was noted in this study, and in other tests with wettable powder formulations.

SENSITIZATION

No evidence of sensitization or anaphylactic shock was noted in guinea pigs given repeated subcutaneous injections of B.t.

I.V. INJECTION

A single I.V. dose of 10^8 B.t. spores was not toxic to young growing rats. There was no evidence of sporulation of B.t. within the visceral tissues over the course of a 112-day experiment.

TOXICITY TO FISH

No adverse effects were shown in rainbow trout and bluegills exposed to B.t. technical material at concentrations of 560 and 1,000 ppm.

A small marine fish, Anguilla anguilla, was not adversely affected by exposure to 1,000-2,000 times the level of B.t. expected during spray programs.

Field observations, one month after aerial application of B.t. revealed no effects on populations of brook trout, common white suckers and smallmouth bass.

TOXICITY TO BIRDS

LD_{50} - Bobwhite Quail - Greater than 10 grams B.t./kg body weight; autopsy of the birds revealed no pathology attributable to B.t.

Field observation of 74 bird species revealed no population fluctuations after aerial application of B.t.

TOXICITY TO BEES

No toxicity to honeybees has been demonstrated during extensive laboratory and field studies with B.t. products at labeled rates.

TOXICITY TO BENEFICIAL INSECTS

No toxic effects to beneficial or predacious arthropods have been observed at labeled rates of B.t. These results are based on laboratory and field studies performed on

over 200 species of beneficial insects/spiders in the orders: Hymenoptera, Diptera, Neuroptera, Orthoptera, Araneae, Coleoptera and Hemiptera. Due to its negligible effects to beneficials and unique mode of action, B.t. is an ideal component of integrated pest management programs.

RESIDUES

Since products containing B.t. have not been shown to be toxic to nontarget organisms, spray drift and residues do not present a health hazard.

TOLERANCE

Dipel has been granted exemption form the requirement of tolerance for specific levels of residues of this organism at the time of harvest on all registered crops in Canada and the United States. The wettable powder formulation may be applied to certain raw agricultural commodities after harvest.

VIRAL ENHANCEMENT

The susceptibility of cell cultures to viral infection was not enhanced after exposure to the HD-1 strain of B.t.

HAZARD EVALUATION SUMMARY

It appears that persons mixing, loading and applying products containing the HD-1 strain of B.t. do not need protective clothing or to follow special protective handling procedures.

It appears that use of this strain of B.t., which occurs naturally in nature, does not pose hazards to man if applied in or over an urban environment.

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State of California

Memorandum

To : Keith T. Maddy, Unit Chief/Staff Toxicologist
Worker Health and Safety Unit

Date : March 5, 1982

Place : Sacramento

From : Department of Food and Agriculture – S. A. Peoples, Medical Consultant
Worker Health and Safety Unit

Subject: Information On The Animal and Human Toxicity Of The Spores of Bacillus thuringiensis Registered Under The Name of Thuricide-HP

One book which covers this subject is "Microbial Control of Insects and Mites" edited by H.D. Burges, and N.W. Hussey, published in 1971 by Academic Press; an updated edition of this book will be available soon.

The initial field work, including safety studies, were carried out between 1956-1958 which included human volunteer tests. On April 14, 1960 the FDA granted full exemption from a tolerance, allowing its use on food and forage crops. The strain of bacteria must not produce a B-exotoxin; the Kurstaki strain which does not produce B-exotoxin is used in Thuricide.

There are strains of B.t. which produce an exotoxin which is toxic to mice and when these bacteria are fed to steers, they are not affected by the exotoxin which is excreted in the feces and killed flies; hence the name "fly factor". Twenty-four grams of Thuricide (2×10^{12} spores) were given orally to rats without evidence of toxicity. Eighteen human volunteers ingested 1 gr/day for 5 days without toxicity and laboratory tests were negative. Five human volunteers inhaled 150 mg of powder daily for 5 days without evidence of illness. All volunteers were examined 4-5 weeks later and were found to be in good health.

The spores have not been found to germinate in mammals or man. The possibility of a new strain developing which is pathogenic to vertebrates is extremely unlikely on a single passage through an animal. (Edward A. Steinhaus, J Econ. Ent. 52:506 (1959)). The possibility of a toxic strain developing during manufacture is monitored as required by law not only for toxic mutations but contamination with any spore-forming bacteria.

The use of B.t. over a 20 year period has not resulted in incidents of toxicity or infection in man or animals. I do not forsee any health problems from its use in controlling the Gypsy Moth in Santa Barbara.

SAP:lm

SURNAME	SAP	Keith T. Maddy			
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INSECTICIDE SAFETY

Toxicology of the Microbial Insecticide, Thuricide

ROBERT FISHER
Bioferm Corp., Wasco, Calif.
LAWRENCE ROSNER
Rosner-Hixson Laboratories, Chicago, Ill.

One of the advantages of the new living insecticide based on the viable spores of the microorganism *Bacillus thuringiensis* Berliner is its nontoxic nature for man, other animals, and plants. This characteristic was firmly established in a series of tests which included an unusual human volunteer test. The toxicology studies described in this paper represented a pioneering effort, as there was no precedent to guide the manufacturer or government officials in establishing that the proposed use of the pesticide would be without hazard to health.

THURICIDE (Bioferm Corp., Wasco, Calif.) is a live pest control agent which is a fatal, quick-acting disease for susceptible insects. The active principle consists of live spores of the microorganism *Bacillus thuringiensis* Berliner, a bacterium first isolated in 1911 from diseased larvae of the Mediterranean flour moth. A review of the literature (*2, 12-18*) reveals no authenticated instance of this true insect pathogen having caused an infectious disease in warm-blooded animals or plants either experimentally or in nature. On December 10, 1958, the Food and Drug Administration authorized the application of the microbial insecticide Thuricide directly to food and forage crops under the conditions of a temporary exemption from a tolerance. Part of the exhaustive 2-year toxicological study which satisfied government officials and the manufacturer as to the safety of Thuricide is described.

Experimental

The toxicological studies on Thuricide were divided into four groups: infectivity and sensitization, acute and chronic toxicity, effect on human volunteers, and toxicity in the field. Some of the tests in the first, second, and third groups are presented here.

The Thuricide used in most of the tests contained approximately 9×10^9 viable spores of *B. thuringiensis* per gram, and in the human volunteer study, 3×10^9 viable spores per gram. Spore count was determined by a plating method (*3*). In addition to the active spores, the product contained a diatomaceous earth filler which had some toxic effect on animals in the massive doses given. When vegetative or sporulated cultures of the microorganism itself were used in these tests, they were designated as *Bacillus thuringiensis* Berliner.

Virulence of Thuricide Following Serial Passage through Mice. One half gram of Thuricide was added to 20 ml. of nutrient broth and incubated at 37° C. for 72 hours. Immediately before injection into the test animals, another 0.5 gram of the sample was added to the incubated material, providing both spores and vegetative forms of the microorganism.

Thirty-five white mice, weighing 17.0 to 23.0 grams, were assembled into seven groups of five mice each. The animals were placed in wire cages and fed a standard mouse diet and water ad libitum. The mice in group 1 were injected intraperitoneally with 1.0 ml. of the prepared material. After 6 hours, 0.3 ml. of blood was withdrawn by cardiac puncture and injected intraperitoneally into group 2. This technique was repeated for a total of six transfers using five more groups of mice. Group 7 was weighed prior to injection and after 24 and 48 hours. No weight losses nor abnormal symptoms during the test period were observed. In group 1, one mouse died within 4 hours after injection of the prepared sample. Gross pathology indicated a severe irritation of the peritoneum. The other mice in this group displayed signs of malaise prior to cardiac puncture.

To determine whether the cause of death and the symptoms observed in group 1 were associated with the carrier in which the microorganisms of the sample were incorporated, the following tests were performed.

One half gram of the sample was incubated in 20 ml. of nutrient broth for 24 hours. A portion of the supernatant liquid was decanted into another tube of nutrient broth and incubated for an additional 48 hours. The resulting cell suspension was then centrifuged and washed twice with isotonic saline solution. This technique resulted in a suspension which was largely free of the carrier material and it contained about 3×10^9 organisms per ml. One milliliter of this suspension was injected intraperitoneally into five mice. No deaths or abnormal symptoms were observed.

One gram of the sample was incubated for 48 hours in 20 ml. of nutrient broth. After incubation, the material was autoclaved. The bacterial cell count was about 3×10^8 nonviable organisms per ml. One milliliter of this material was injected intraperitoneally into five mice. All of the five mice died within 16 hours, displaying symptoms of abdominal irritation and sensitivity.

One milliliter of the nutrient broth was injected intraperitoneally into five mice. No deaths or abnormal symptoms were observed.

Although direct intraperitoneal injection of Thuricide into mice caused toxic symptoms, this effect was due to the carrier only. The organisms themselves had no toxic effect, nor was any virulence developed by serial passage through mice.

Persistence of *B. thuringiensis* in Blood of Mice Following Intraperitoneal Injection. Sixty white mice weighing 17 to 33 grams were assembled into six groups of 10 mice each. The animals were held in wire cages and fed a standard laboratory mouse diet and water ad libitum. Groups 1, 2, and 3 were injected intraperitoneally with 0.1 ml. of a 24-ml. nutrient broth culture of *B. thuringiensis*. Groups 4, 5, and 6 were injected with 0.1 ml. of a 24-hour broth culture of *B. cereus*, an organism which is generally considered as nonpathogenic under most conditions and is morphologically related to *B. thuringiensis*. This organism was included for comparative purposes.

Blood samples, 0.3 ml., were withdrawn by cardiac puncture from groups 1 and 4 after 24 hours, from groups 2 and 5 after 48 hours, and from groups 3 and 6 after 72 hours. Each blood sample was plated on tryptone glucose extract agar and the resulting *B. thuringiensis* or *B. cereus* colonies were counted.

The plate counts showed that both organisms persisted in the blood up to 48 hours. However, as neither organism was found at 72 hours, the persistence of *B. thuringiensis* was no greater than that of the strain of *B. cereus* used in this test.

Determination of Relative Pathogenicity of *B. thuringiensis* by Parenteral Administration into Guinea Pigs. The pathogenicity of *B. thuringiensis* for guinea pigs was compared with that of *B. cereus* and of *B. subtilis*, both considered to be nonpathogenic under most conditions. The method employed was that of Clark (*5*). The test organisms were cultured in glucose broth for 24 hours before injection. To obtain higher concentrations of organisms, 24-hour glucose agar slants were prepared and the organisms were washed off with 1 ml. of saline.

The groups of guinea pigs injected with the 24-hour broth culture received 4 ml. each. The groups injected with the slant washings received 1 ml. containing the growth from one slant. All injections were intraperitoneal. The animals were observed for 7 days after injection. Data are shown below.

Organism	Type of Culture	No. of Animals Injected	No. of Animals Surviving
B. thuringiensis	Broth	10	10
	Slant	10	3
B. cereus	Broth	5	5
	Slant	5	0
B. subtilis	Slant	5	5

Massive doses of the microorganisms are required to overcome the guinea pigs defense mechanism, because injection of the broth cultures caused no fatalities.

Inhalation Toxicity of *B. thuringiensis* Berliner in Mice. Inhalation toxicity was determined by placing 10 mice identified as Test Group 1, in an exposure chamber 30 × 30 × 30 cm. and dispersing Thuricide with a powder blower by means of compressed air. The animals were subjected to four exposures over a period of 6 days. The duration of each exposure was 15 minutes, during which time 10 grams of sample were dispersed. Between exposures the animals were housed in wire cages and were fed laboratory mouse diet and water ad libitum. The mice were weighed initially and at the end of the test. Observations were made of their reaction in the exposure chamber as well as of their general well-being throughout the test period.

In order to determine whether irritation to the lungs might result from the inhalation of only the carrier in which the active ingredient of the sample was incorporated, a portion of the test sample was sterilized by autoclaving and another group of 10 mice was subjected to the same exposure.

During repeated exposures of the mice to inhalation of the test material, no untoward reaction was observed in either group. Observations of their general well-being throughout the test period showed no departure from normal in either group, as was demonstrated also by normal weight gains for both groups. Gross pathology findings were negative.

The Allergenicity of Thuricide in Guinea Pigs. The procedure of Draize, Woodward, and Calvery (*6*) was employed for the determination of the allergenicity of Thuricide. Twenty white male guinea pigs were distributed into two groups of eight each and one group of four. The hair was removed from the back and flanks by close clipping. The sample was tested by the following methods.

Injection of a 0.1% Suspension in Water. Injections were made intracutaneously using a 25-gage needle. Ten sensitizing doses were administered, by injection, every other day for 3 weeks. Sites of injection were at random over the backs and flanks. The first injection was 0.05 ml., while the other nine contained 0.1 ml. each. Eight animals were used.

Topical Application on Abraded Skin. Ten sensitizing applications were administered every other day for 3 weeks. The abrasion for each application was made, at random, on the backs and flanks. The test material was applied with a powder blower, covered with an aluminum patch and taped in place. The first application was approximately 25 mg., while the other nine were approximately 50 mg. each. Eight animals were used.

Topical Application to Intact Skin. Ten applications were made in the same manner as on the abraded skin, except that the skin was left intact. Four animals were used.

Readings were taken 24 hours after the first application or injection to record any initial allergenic response as evidenced by the development of erythema and/or wheal formation. Two weeks after the tenth application or injection the challenge injection or application was made in the region of the lower flank, where no previous application had been made. The challenge dose was the same as that given in the first sensitizing dose. Twenty-four hours later readings were taken again for correlation with those obtained after the first injection or application.

Administration of Thuricide by injection or by application to abraded skin caused a slight erythema and edema, indicative of local irritation. There was no reaction from its application on intact skin. There was no evidence of any allergenic response by any route of administration.

Inhalation and Ingestion of Thuricide by Human Volunteers. Eighteen human subjects were employed in this experiment. All of the individuals were subjected to physical and laboratory examinations immediately before the start of the experiment. They then ingested 1 gram of the Thuricide in capsules daily for 5 days. In addition to oral ingestion, five of the subjects inhaled 100 mg. of the powder daily for 5 days. Inhalation was from an inhaler device (Abbott's inhalator) and both oral ingestion and nasal inhalation were used on alternate days. At the end of the 5-day test period, the subjects again received physical and laboratory examinations and again in 4 or 5 weeks later. In addition to these tests, the individuals who inhaled the insecticide also were subjected to x-ray examinations at the same intervals.

The physical examinations included a detailed history and records of height, weight, temperature, blood pressure, respiratory rate, pulse rate immediately after exercise and 30 and 60 seconds thereafter, and vital capacity (in the inhalation group). They also included evaluations of the genitourinary, the gastrointestinal, the cardiorespiratory, and the nervous sytems. Laboratory tests included routine urinalysis, with qualitative and quantitative (when indicated) urobilinogen determination, complete blood count, sedimentation rate, blood urea nitrogen, glucose, bilirubin, and thymol turbidity tests. All of the subjects remained well during the course

of the experiment. All laboratory findings were negative.

Determination of Hazard to Humans from Continued Random Exposure to Thuricide. Eight Bioferm employees in different parts of the manufacture and control of Thuricide production were observed during a 7-month exposure to:

WHOLE FERMENTATION BROTH. Exposures of 300 ml. to several thousand gallons per day.

MOIST BACTERIAL CAKE. Exposures of 50 grams to several thousand pounds per day.

EFFLUENT. Exposures from 300 ml. to several thousand gallons per day.

FINAL POWDER. It contained up to 15×10^9 viable spores per gram. Exposures of 10 grams to several thousand pounds per day. This material is ground, blended, and packaged. It is finely divided and dusts easily.

The formal record of the eight employees during exposure was free of complaints of any kind. Two of the employees who had been exposed to a greater extent than any of the others (total exposure 251 hours to all phases of production and control) were given comprehensive medical examinations. The two subjects were in excellent health and showed no evidence of chronic or acute damage of any kind from exposure to materials handled in the plant. The results of this record indicate that no hazard to health exists from prolonged and continued exposure to broths, moist cakes, or powders of Thuricide.

Acute Oral Toxicity of Thuricide. Thuricide was administered to rats in a 33% suspension in water containing 1% of carboxymethyl cellulose as a thickener. Administration was made by means of a syringe, having attached a hypodermic needle with a ball tip. The dose was placed directly into the animal's stomach. Doses up to 24 grams of Thuricide—estimated 2×10^{12} viable spores—per kilogram of body weight were administered to groups of 10 rats and the animals were observed for 1 week. No fatalities occurred nor were there any outward symptoms of toxicity. Gross and histological examination of tissues revealed no differences from the tissues of control animals.

Discussion

The tests which have been described have emphasized the harmlessness of the microbial insecticide Thuricide, and the active ingredient, *B. thuringiensis* Berliner, for warm-blooded, animals. The results of these tests partially satisfied the toxicity requirements of the Food and Drug Administration.

In addition, the area of lack of toxicity has been considerably extended in reports from other laboratories (*1*, *4*, *7–9*). This further work has included acute and chronic toxicity tests with chicks, laying hens, young swine and hogs, fish, adult honey bees, and honey bee larvae. In one of these tests (*4*), a group of New Hampshire Red laying hens received as part of their diet a daily supplement of 0.5 to 10 grams of Thuricide for 23 months. No significant differences in weight, appearance, or egg number and quality were observed between the test and control groups of laying hens.

One of the recurring questions about the harmlessness of *B. thuringiensis* to warm-blooded animals has been the important matter of the taxonomic grouping of this microorganism in the same genus with *Bacillus anthracis*. The morphological similarity of these two microorganisms is the basis for this classification. However, this does not by any means indicate that the characteristics of the two are interchangeable. The specific questions have been whether these two microorganisms can be confused with one another or mutate into virulent forms, and not whether *B. thuringiensis* has any of the virulent characteristics of *B. anthracis*. These questions have been answered, in the negative, in a full discussion by Steinhaus (*10*). In the manufacture of Thuricide during the last $2^1/_2$ years, no instance has been found of accidental contamination, or of mutation of *B. thuringiensis* into a virulent form for man, animals, or plants (*3*, *10*). In addition to the rigid quality control procedures applied (*3*), the final definitive test before the release of any batch of Thuricide is a mouse safety test described by Simmons and Gentzkow (*11*).

Finally, there have been no reports of toxicity of any kind to plants, animals, beneficial insects, or humans during the field application of nearly 1000 pounds of Thuricide in the 1957 and 1958 seasons.

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